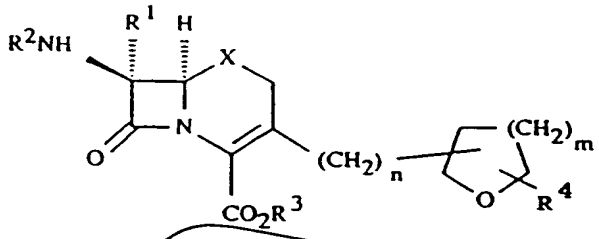
Claims

1. A compound of formula (I) or a salt thereof:



(I)

wherein

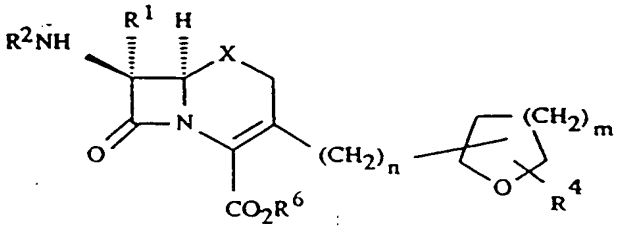
R^1 is hydrogen, methoxy or formamido;

R^2 is an acyl group;

CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group;

R^4 represents up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S, SO, SO_2, O or CH_2; m is 1 or 2; and n is O.

2. A compound as claimed in claim 1 having the formula (Ia):

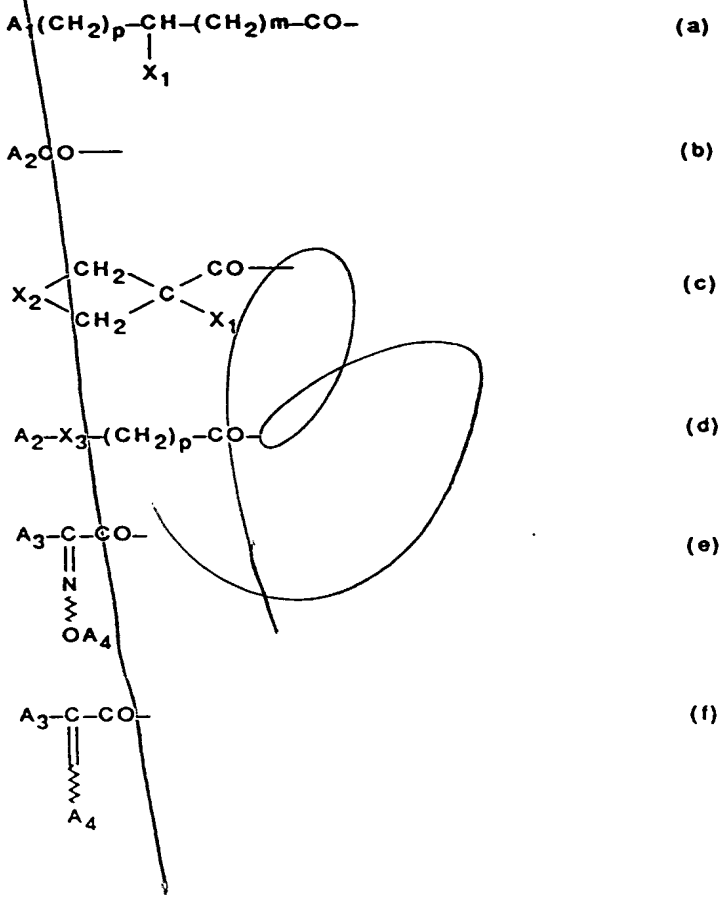


(Ia)

wherein R^1, R^2, R^4, m, n and X are as defined with respect to formula (I) in claim 1 and the group CO_2R^6 is CO_2R^3 where CO_2R^3 is a carboxy group or a carboxylate anion, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

3. A compound as claimed in claim 1 or claim 2 wherein R^1 is hydrogen.

4. A compound as claimed in claim 1,2 or 3 wherein R^2 is an acyl group of formula (a) to (f):



(a)

(b)

(c)

(d)

(e)

(f)

wherein p is 0, 1 or 2; m is 0, 1 or 2; A_1 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic or heteroaromatic group; X_1 is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group; A_2 is an aromatic or heteroaromatic group, a substituted alkyl group; or a substituted dithietane; X_2 is a $-CH_2OCH_2-$, $-CH_2SCH_2-$ or alkylene group; X_3 is an oxygen or sulphur atom; A_3 is an aryl or heteroaryl group; and A_4 is hydrogen, C_{1-6}alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-6})alkyl, C_{1-6} alkoxycarbonyl(C_{1-6}) alkyl, C_{2-6} alkenyl, carboxy(C_{1-6})alkyl, C_{2-6} alkynyl, aryl or C_{1-6}alkyl substituted by up to three aryl groups.

5. A compound as claimed in claim 4 wherein A_1 is optionally substituted phenyl, X_1 is hydrogen or amino, A_2 is optionally substituted phenyl, X_3 is oxygen , A_3 is aminothiazolyl, aminothiadiazolyl or furyl, and R_4 is hydrogen, C_{1-6} alkyl, or carboxy C_{1-6} alkyl.

6. A compound as claimed in any one of claims 1 to 5 wherein CO_2R^3 is carboxy or a carboxylate anion or R^3 is t-butyl, 4-methoxybenzyl, diphenylmethyl, acetoxymethyl, acetoxyethyl, pivaloyloxymethyl, propan-2-yloxycarbonyl-oxyethyl or 2-ethoxycarbonyl-but-2-enyl.

7. A compound as claimed in any one of claims 1 to 6 wherein the cyclic ether group bonded to the 3-position of the cephalosporin nucleus is unsubstituted or unsubstituted by up to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyloxy C_{1-6} alkyl or C_{1-6} alkoxy C_{1-6} alkyl.

8. A compound as claimed in any one of claims 1 to 7 wherein m is 1.

9. A compound as claimed in any one of claims 1 to 8 wherein the cyclic ether group is a tetrahydrofuran-2-yl or a tetrahydropyran-2-yl group.

10. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

11. Pivaloyloxymethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

12. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydropyran-2-yl]-ceph-3-em-4-carboxylate.

13. Pivaloyloxymethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.

14. (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylic acid.

15. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

16. Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

17. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

18. Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

19. Diphenylmethyl (6R,7R)-7-phenylacetamido-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

20. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido-3-[(RS)-tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.

21. Acetoxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

22. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxymethyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate

23. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-(Z)-pent-2-enamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

24. Sodium (6R,7R)-7-[2-(2-Aminothiadiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

25. (RS)-1-Acetoxyethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

26. (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-carboxymethoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylic acid disodium salt.

27. Sodium (6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)-acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

28. Sodium (1S,6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1-oxide.

29. Sodium 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(tetrahydrofuran-2-yl)-1-carba-1-dethia-ceph-3-em-4-carboxylate.

30. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxy-iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1,1-dioxide.

31. (RS)-1-(Propan-2-yl)oxycarbonyloxyethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

32. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(5R,2SR)-5-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

33. Sodium (6R,7R)-7-[2-(furan-2-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

34. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-5,5-dimethyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

35. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxycarbonyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate]

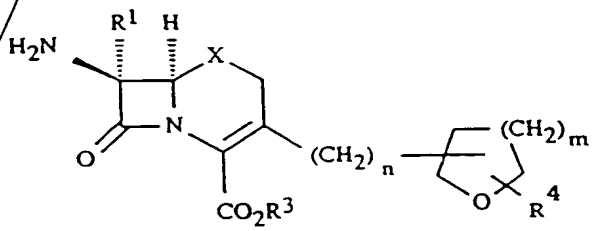
36. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[3-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

37. 2-Ethoxycarbonyl-(Z)-but-2-enyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetomido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

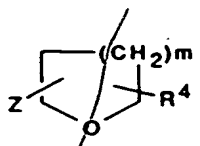
38. A compound of formula (I) as defined in claim 1 substantially as hereinbefore described with reference to the preparative examples.

39. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 28 which process comprises:

(a) treating a compound of formula (II) or a salt thereof:



(II)



(XI)

wherein Z is an organo-cuprate group and R^4 and m are as hereinbefore defined with respect to formula (I) in claim 1;

and thereafter, if necessary or desired, carrying out one of the following steps:

i) removing any protecting groups;

ii) converting the group CO_2R^3 to a different group CO_2R^3;

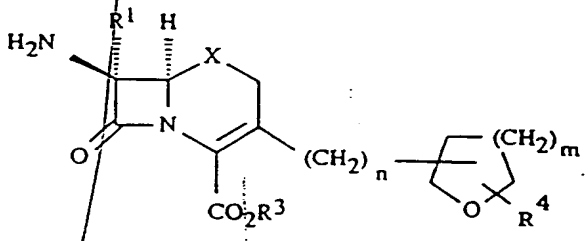
iii) converting the group R^2 to a different group R^2;

iv) converting the group X to a different group X;

v) converting the product into a salt.

40. A process for the preparation of a compound of formula (I) substantially as hereinbefore described in the preparative Examples.

41. A compound of formula (II) or a salt thereof:



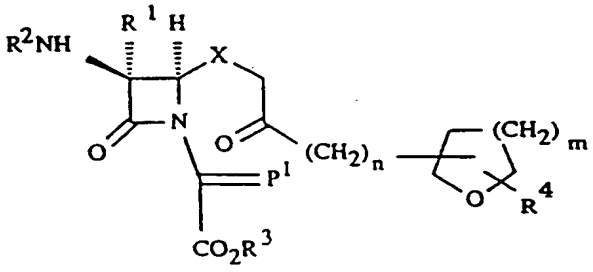
(II)

wherein R^1, CO_2R^3, R^4, m, n, and X are as hereinbefore defined with respect to formula (I) in claim 1, wherein any reactive group may be protected, and wherein the amino group is optionally substituted with a group which permits acylation to take place, with an N-acylating derivative of an acid of formula (III):

$$R^2OH \qquad \text{(III)}$$

wherein R^2 is as hereinbefore defined with respect to formula (I) in claim 1 and wherein any reactive group may be protected; or

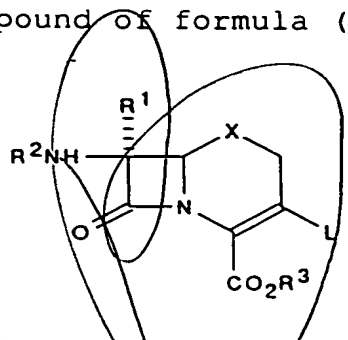
(b) cyclising a compound of formula (IV):



(IV)

wherein X, R^1, R^2, R^4, m, n and CO_2R^3 are as hereinbefore defined with respect to formula (I) in claim 1 and P' is a phosphorus residue; or

(c) treating a compound of formula (X):



(X)

wherein R^1, R^2, CO_2R^3 and X are as hereinbefore defined with respect to formula (I) in claim 1, and L is a leaving group, with a compound of formula (XI):

wherein R^1 CO_2R^3, R^4, X, m and n are as hereinbefore defined with respect to formula (I) in claim 1.

42. t-Butyl 6R,7R-7-Amino-3-(tetrahydrofuran-2-yl)--ceph-3-em-4-carboxylate.

43. t-Butyl (6R,7R)-7-Amino-3-[(RS)-tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.

44. 4-Methoxybenzyl (6R,7R)-7-amino-3-(tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

45. Pivaloyloxymethyl (6R,7R)-7-amino-3-(tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

46. t-Butyl (6R,7R)-7-Amino-3-[(RS)-tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.

47. Acetoxymethyl (6R,7R)-7-amino-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

48. 4-Methoxybenzyl (6R,7R)-7-Amino-3-(5-methoxymethyl-tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

49. 4-Methoxybenzyl (6RS,7SR)-7-amino-3-(tetrahydrofuran-2-yl)-1-carba-1-dethiaceph-3-em-4-carboxylate.

50. 4-Methoxybenzyl (6R,7R)-7-amino-3-(5-methyl-tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

51. A compound of formula (II) as defined in claim 41 substantially as hereinbefore described with reference to the preparative Examples.

52. A pharmaceutical composition comprising a compound of formula (Ia) as defined in claim 2 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, and a pharmaceutically acceptable carrier.

53. A pharmaceutical composition as claimed in claim 52 further comprising a β-lactamase inhibitor.

54. A compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined in claim 2, for use as a therapeutic agent.

55. A method of treating bacterial infections in humans and animals which comprises administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, to a human or animal.

56. The use of a compound of formula (Ia) or a pharmaceutially acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, for the manufacture of a medicament for the treatment of bacterial infections.